Cell Type-Specific Chromatin Signatures Underline Regulatory DNA Elements in Human Induced Pluripotent Stem Cells and Somatic Cells.

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Public Summary:

Scientific Abstract:
RATIONALE: Regulatory DNA elements in the human genome play important roles in determining the transcriptional abundance and spatiotemporal gene expression during embryonic heart development and somatic cell reprogramming. It is not well known how chromatin marks in regulatory DNA elements are modulated to establish cell type-specific gene expression in the human heart. OBJECTIVE: We aimed to decipher the cell type-specific epigenetic signatures in regulatory DNA elements and how they modulate heart-specific gene expression. METHODS AND RESULTS: We profiled genome-wide transcriptional activity and a variety of epigenetic marks in the regulatory DNA elements using massive RNA-seq (n=12) and ChIP-seq (chromatin immunoprecipitation combined with high-throughput sequencing; n=84) in human endothelial cells (CD31(+)CD144(+)), cardiac progenitor cells (Sca-1(+)), fibroblasts (DDR2(+)), and their respective induced pluripotent stem cells. We uncovered 2 classes of regulatory DNA elements: class I was identified with ubiquitous enhancer (H3K4me1) and promoter (H3K4me3) marks in all cell types, whereas class II was enriched with H3K4me1 and H3K4me3 in a cell type-specific manner. Both class I and class II regulatory elements exhibited stimulatory roles in nearby gene expression in a given cell type. However, class I promoters displayed more dominant regulatory effects on transcriptional abundance regardless of distal enhancers. Transcription factor network analysis indicated that human induced pluripotent stem cells and somatic cells from the heart selected their preferential regulatory elements to maintain cell type-specific gene expression. In addition, we validated the function of these enhancer elements in transgenic mouse embryos and human cells and identified a few enhancers that could possibly regulate the cardiac-specific gene expression. CONCLUSIONS: Given that a large number of genetic variants associated with human diseases are located in regulatory DNA elements, our study provides valuable resources for deciphering the epigenetic modulation of regulatory DNA elements that fine-tune spatiotemporal gene expression in human cardiac development and diseases.